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EXAMINER	
SCHLAPKOHL, WALTER	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/740,079	SINGH ET AL.	
	Examiner	Art Unit	
	Walter Schlapkohl	1636	waf

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *11 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *24-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/18/2003 & 5/19/2004* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/6/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the papers filed 7/11/2005. Claims 1-31 are pending.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-23) in the reply filed on 7/11/2005 is acknowledged.

Claims 24-31 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 7/11/2005.

The requirement is deemed proper and is therefore made FINAL.

Information Disclosure Statement

The information disclosure statement filed 7/6/2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be

listed; and all other information or that portion which caused it to be listed. Those references for which copies were provided have been considered as indicated on the returned form PTO-1449.

Drawings

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: with the exception of Figure 4, all of the figures (Figures 1-3 & 5-17) contain reference characters not identified in the brief description of the drawings. Furthermore, the references to Figures 7 and 8 on page 24 of the specification are incorrect. Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d).

If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

Claim 14 is objected to because of the following informalities: claim 14 recites "the first detection group D_1 is exemplified as a cephalosporin" and should instead read "as a coumarin". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 7, 11-12, 14, 17-18 & 23, and therefore dependent claims 2-6, 8-10, 13, 15-16 & 19-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 11-12, 14 and 17 recite "separation modifier" or "separation modifiers". Claims 1, 11-12, 14 and 17 are vague and indefinite in that it is unclear what is meant by a separation modifier. Is a separation modifier any moiety that confers a "separation characteristic" upon a probe by means of capillary electrophoresis or may any means of electrophoretic separation be employed?

Claim 7 recites "wherein said incubating is carried out in a single well containing a plurality of different cells, each containing a different probe" in lines 1-3. Claim 7 is vague and indefinite in that it is unclear whether the cells are different types of cells or whether the cells are different because they each contain different probes.

Claim 7 recites "said obtaining includes obtaining released tags from the cells in said well" in lines 3-4. Claim 7 is vague and indefinite in that it is unclear whether the tags are released from their binding moieties within the cell or whether the tags are released into the extracellular milieu or both.

Claim 12 recites "where exemplary positions of transport moieties are shown as T_1, T_2 and T_3" in lines 3-4. Claim 12 is vague and indefinite in that T_3 does not appear in the pictured structure of the probe.

Claim 12 recites "a substrate for the enzyme, S, is exemplified as a four-member β-lactam ring" in lines 8-9. Claim 12 is vague and indefinite in that it is unclear whether the enzyme or the substrate has been given the designation "S".

Claim 17 recites "the action of the enzyme on the probe produces an e-tag reporter of the form (D, M)- S', where S' is the residue of the substrate remaining with the e-tag reporter after reaction of S with the enzyme" in lines 6-8. Claim 17 is vague and indefinite in that there is no antecedent basis for "the residue".

Claim 18 recites "(ii) cell contains said first and second hybrid proteins" in line 8. Claim 18 is vague and indefinite in that it is unclear which cell is being referred to: a particular transfected cell or a group of cells from a particular well or some other cell?

Claim 23 recites "[t]he method of claim 21…thereby determining the effect of the compound on interaction between any of the hybrid protein and the designated DNA sequence". Claim 23 is vague and indefinite in that there is only one hybrid protein referred to in claim 21.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a multiplexed assay for monitoring the level of transcription of one or more genes in response to one or more potential regulatory stimuli, comprising: placing transfected cells in each of a plurality of wells, where the cells in each well are transfected with a genetic construct comprising a selected promoter operatively linked to the coding sequence for an enzyme having a selected enzyme activity; adding to the cells in each well a probe selected from a set of probes where each probe in the set is cleavable by the enzyme into a substrate moiety and an electrophoretic tag (e-tag) reporter having a detection group and a separation modifier that confers on the e-tag reporter a unique electrophoretic mobility with respect to the e-tag reporters derived from the other probes in

the set; incubating the cells and associated probes while exposing the cells to a potential regulatory stimulus; obtaining the tags from the cells; electrophoretically separating the conbined tags; and determining from the electrophoretic mobility and level of detection group of each separated e-tag reporter, the level of transcriptional response of each cell to the potential regulatory stimulus to which the cells were exposed. The claims encompass any enzyme having a selected enzymatic activity and any probe from a set of probes, where each probe in the set is cleavable by the enzyme into a substrate moiety and an electrophoretic (e-tag) reporter having a detection group and a separation modifier that confers on the e-tag reporter a unique electrophoretic mobility with respect to the e-tag reporters derived from the other probes in the set. The claims do not provide any structural information with regard to the enzyme sequences (or nucleic acid sequences encoding such enzymes) capable of cleaving probes such that the level of transcriptional response of each cell to the potential regulatory stimulus to which the cells were exposed is determined from the electrophoretic mobility and level of detection group of each separated e-tag reporter. Thus, the rejected claims thus comprise a set of nucleic acid sequences that are defined by the function of the encoded protein.

Neither do the claims provide any structural information regarding which probes can be used with which enzyme except for β-lactamase and the two probes set forth in Figures 6 and 8. Finally, the rejected claims encompass a set of separation modifiers as part of each e-tag reporter. No structural information is provided for a separation modifier except for those referred to in Figure 4.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification describes a β-lactamase enzyme capable of cleaving two different probes as set forth in Figures 6 and 8. No description is provided of a single enzyme sequence. No other probes are described for use with any other enzymes. No mention is made of which separation modifiers could be attached to which probes.

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only representative of one enzyme capable of cleaving a probe with

the recited limitations. The results are not necessarily predictive of any other enzyme capable of cleaving the disclosed probes such that the level of transcriptional response of each cell to the potential regulatory stimulus to which the cells were exposed is determined from the electrophoretic mobility and level of detection group of each separated e-tag reporter. Thus, it is impossible to extrapolate from the examples described herein those enzymes that would necessarily meet the structural/functional characteristics of the rejected claims.

The prior art does not appear to offset the deficiencies of the instant specification in that it does not describe a set of enzymes that are capable of cleaving the disclosed probes such that the level of transcriptional response of each cell to the potential regulatory stimulus to which the cells were exposed is determined from the electrophoretic mobility and level of detection group of each separated e-tag reporter. Zlokarnik et al (Science 279:84-88) describe a βlactamase enzyme capable of fulfilling such limitations, but its use is limited to the CCF2/AM probe and this probe has no separation modifier.

Given the very large genus of nucleic acid molecules encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to the enzyme sequences capable of fulfilling the claim

limitations of claims 1-10 and 15-23, the skilled artisan would not have been able to describe the broadly claimed genus of enzymes capable of cleaving the disclosed probes such that the level of transcriptional response of each cell to the potential regulatory stimulus to which the cells were exposed is determined from the electrophoretic mobility and level of detection group of each separated e-tag reporter. Also, given the very large genus of probes encompassed by the rejected claims, and given the limited description provided by the prior art and the specification with regard to the probe structures comprising separation modifiers capable of fulfilling the claim limitations of claims 1-23, the skilled artisan would not have been able to describe the broadly claimed genus of probes cleavable by such enzymes. Thus, there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those nucleic acid sequences, probes and separation modifiers that satisfy the functional limitations of the claims. Therefore, the skilled artisan would have reasonably concluded applicants were not in possession of the claimed invention for claims 1-23.

Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described

in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, the relative skill levels of those in the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The rejected claims are drawn toward a method of monitoring the level of transcription of one or more genes in response to one or more potential regulatory stimuli comprising: placing transfected cells in each of a plurality of wells, where the cells in each well are transfected with a genetic construct comprising a selected promoter operatively linked to the coding sequence for an enzyme having a selected enzyme activity; adding to the cells in each well a probe selected from a set of probes where each probe in the set is cleavable by the enzyme into a substrate moiety and an e-tag reporter having a detection group and a separation modifier that confers on the e-tag reporter a unique electrophoretic mobility

with respect to the e-tag reporters derived from the other probes in the set; incubating the cells and associated probes while exposing the cells to a potential regulatory stimulus; obtaining the tags from the cells; electrophoretically separating the conbined tags; and determining from the electrophoretic mobility and level of detection group of each separated e-tag reporter the level of transcriptional response of each cell to the potential regulatory stimulus to which the cells were exposed. The invention is complex in that it involves transfecting cells with a genetic construct encoding an enzyme operatively linked to a promoter. Additionally, the transfected cells are incubated in the presence of a probe and one or more potential regulatory stimuli. The probe must cross the plasma membrane and be retained in the cytoplasm. Expression of the enzyme is monitored in a complex process which requires the expression of an active enzyme with a selected activity (presumably cleavage of the probe). Cleavage of the probe into a substrate moiety and an e-tag reporter having a detection group and a modifier allows for separation of the e-tags, once obtained from the cells, via their electrophoretic mobility. The level of activity of the enzyme (and hence the activity of the operatively linked promoter in response to the given stimulus/stimuli) can then be determined based upon "the

level of detection group" of each separated e-tag reporter. Enzymes recognize very specific substrate constructs and the nature of the enzyme-substrate interaction can affect the rate of the reaction; therefore, the complex nature of the invention is increased by the complex nature of enzyme-substrate interactions. Which probe structures, then, would allow for the proper enzyme-substrate interactions such that transcription of a gene or set of genes from a given promoter or promoters could be monitored? Which separation modifier structures would allow for such enzyme-substrate interactions as well as separation by electrophoresis?

Breadth of the claims: The claims are very broad in that they encompass any enzyme having a selected enzymatic activity and any probe wherein the probe is cleavable by the enzyme into a substrate moiety and an e-tag reporter having a detection group and a separation modifier that confers on the e-tag reporter a unique electrophoretic mobility with respect to the e-tag reporters derived from other probes of a set of probes. The e-tag reporter can comprise any moiety such that the separation modifier allows for separation upon electrophoresis. Furthermore, the claims include any promoter operatively linked to any enzyme and the assay method may be performed in any cell

to monitor the response (transcription level change) to any of one or more regulatory stimuli.

Guidance of the specification/The existence of working examples: The specification teaches two probes which can be cleaved by the enzyme β-lactamase. The specification also teaches numerous e-tag reporters which are derived from probes which can be cleaved by a nuclease. However, the specification does not teach one working example of a method for monitoring the transcription of one or more genes in response to one or more potential regulatory stimuli comprising the recited steps of claim 1. No specific teachings are provided with regard to which transport moieties should be combined with which detection groups/separation modifiers such that the level of transcription of one or more genes can be determined by the electrophoretic mobility and level of detection group of each separated e-tag reporter. No specific teachings are provided with regard to the determination of the level of transcriptional response of each cell to the potential regulatory stimulus to which the cells were exposed and the separation of the combined e-tag reporters and how the level of transcription can be correlated. For example, how can the ACLA001 and ACLA017 e-tag reporters in Figure 4 be used to monitor the level of transcription of the gene for a kinase operatively linked to the kinase's promoter in

response to one or more potential stimuli? What device would be used to separate the generated e-tag from these specific probes and how would the level of transcription be assessed, i.e. how would the "level of detection group of each separated e-tag reporter from the ACLA001 and ACLA017 probes and their respective electrophoretic mobility" determine the transcription level of the kinase operatively linked to the kinase's promoter? Could any enzyme or even any nuclease be used in any cell in which the experiment were performed?

State of the art: At the time of Applicant's invention, the art of monitoring the level of transcription of one more genes in response to one or more potential regulatory stimuli utilizing an enzyme and a probe wherein the probe is from a set of probes that can be cleaved by an enzyme into a substrate moiety and an e-tag reporter having a detection group and a separation modifier that confers on the e-tag reporter a unique electrophoretic mobility with respect to the e-tag reporter derived from the other probes in the set was underdeveloped. Zlokarnik et al (Science 279:84-88, 1998) teach the use of a CCF2/AM cephalosporin substrate for β-lactamase to quantitate the level of transcription from the NF-AT promoter (see page 86, column 3). However, Zlokarnik et al do not teach determination of the level of transcription in response to a regulatory

stimulus by the level of detection group of each separated e-tag reporter and electrophoretic mobility. Moreover, Zlokarnik et al do not teach a multiplex assay utilizing a set of probes and separation of the probes using a separation modifier.

Predictability of the art and the amount of experimentation necessary: In an article published post-filing of the instant application, Chan-Hui et al (Clinical Immunology 111:162-174, 2004) teach an e-tag assay system for gene expression that "combines multi-analyte analysis with the high sensitivity of quantification by capillary array electrophoresis (CE)" (see page 163, first column). Chan-Hui et al also teach that the assay system is based on proprietary *eTag*™ reporters that are distinct fluorescent small molecules each of which has unique migration properties in CE analysis. Chan-Hui et al teach that *eTag*™ assays have been developed for multiplex analysis of tens of gene targets in a single reaction and that, for gene expression, *eTag*™ assays "adopt the isothermal linear amplification mechanism based on Cleavase activity (Third Wave Technologies), minimizing any quantitative aberrations that may occur in early cycles of the exponential amplification in PCR" (page 163, first column). Given the potential pitfalls inherent in the invention, such as quantitative aberrations that may occur in early cycles of the exponential amplification in PCR,

it is clear that one skilled in the art would be required to conduct a number of experiments to determine which enzymes could be used with which probes in order to monitor the level of transcription of one or more genes in response to one or more potential regulatory stimuli. This unpredictability is exacerbated by the large genus of enzymes and probes claimed.

Conclusion

Certain papers related to this application may be submitted to the Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is (571) 273-8300. Note: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at (800) 786-9199.

Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should be directed to Walter A. Schlapkohl whose telephone number is (571) 272-4439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM. A phone message left at this number will be responded to as soon as possible (i.e., shortly after the examiner returns to his office.)

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached at (571) 272-0781.

Walter A. Schlapkohl, Ph.D.
Patent Examiner
Art Unit 1636

December 21, 2005

DAVID GUZO
PRIMARY EXAMINER